Clinical characteristics and outcome of tumor-associated acute pancreatitis: a single-center cohort study

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Background: What features should alert clinicians to suspect underlying tumors in patients with acute pancreatitis (AP) was largely unknown. This study aimed to assess the clinical characteristics and outcome in patients with tumor-associated AP.

Methods: Patients who presented with AP and were diagnosed with tumor after admission were included according to the inclusion and exclusion criteria and followed up by hospital notes, telephone, WeChat and/ or e-mail. The clinical characteristics and outcome were analyzed with multivariable logistic regression and were compared with AP patients without tumor.

Results: Out of a cohort of 1,792 AP patients we identified 103 who had a neoplastic etiology. The 103 patients had a median age of 57 (range, 13–81) and 65 were males. AP was mild in 92 patients, moderately severe in 7 and severe in 4. The three most common tumors included pancreatic cancer (PC) (40), periampullary carcinoma (PAC) (25), and neoplastic pancreatic cysts (NPC) (22). The following ranked features were predictive of a tumor etiology: dilation of main pancreatic duct (MPD) (OR 417.83, 95% CI: 80.40–2,171.42), vascular invasion (OR 82.04, 95% CI: 6.05–1,113.14), mild AP (8.29, 95% CI: 1.98–34.73), and anemia (OR 5.73, 95% CI: 2.02–16.26). The median survival period of AP patients with PC, PAC, and NPC was 10.0 (7.0–23.5), 21.0 (5.0–37.0), and 35.0 (30.0–96.0) months, respectively.

Conclusions: Mild AP patients with dilation of MPD, vascular invasion, and anemia were more frequently suggested a tumor etiology. Thus, clinical vigilance is needed for timely detection of tumor-associated pancreatitis with these characteristics.

Keywords: Acute pancreatitis (AP); tumor; retrospective study

Introduction

Acute pancreatitis (AP), an inflammatory disorder of the pancreas, is the leading cause for acute admission among gastrointestinal disorders worldwide (1). The etiology of AP is complex and about 10% of patients are idiopathic with the exclusion of all the common causes (2). Follow-up of these cases may lead to tumors and it was reported that AP might be an early manifestation of many types of tumors, including pancreatic cancer, ampullary carcinoma, intraductal papillary mucinous neoplasms (IPMN), non-Hodgkin lymphoma (NHL), metastatic lung cancer, and parathyroid carcinoma (3-8). Disappointingly, most were case reports, and there was a lack of data regarding typical presentations and diagnostic clues (such as elderly, mild AP) in the early stage of those tumors. While AP might, if appropriately investigated, lead to the earlier diagnosis and better outcome of a pancreatic tumor, it can also result in a delay in diagnosis if clinicians are less vigilant. Any delays, especially for pancreatic adenocarcinoma cases, can adversely impact survival, resulting in late stage of tumor, poor quality of life and short survival time, etc. (9).

This study aimed to analyse a single-center experience with the management of tumor-associated acute pancreatitis, with a particular focus on clinical characteristics and outcome. We presented the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7196).

Methods

Patients and settings

We retrospectively reviewed the electronic medical records of patients with a tumor who presented with AP as the primary admission diagnosis at Peking Union Medical College Hospital in Beijing, China, from 1 January 2000 to 1 December 2018. Eligible patients had the discharge diagnoses of both AP [ICD 10 code (K85)] and tumor [ICD 10 code (C00)-(D48)]. Inclusion criteria: patients had to present with AP and the diagnosis of tumor was made after the onset of AP. The diagnosis of AP was based on the American College of Gastroenterology guidelines (10), which should fulfil at least two of the following three criteria: (I) abdominal pain characteristic of AP, (II) serum lipase equal to or higher than three times the upper normal limit, and (III) characteristic findings of AP on radiologic exams. All the selected patients with tumors had histological confirmation from surgical specimens or fine needle biopsy.

Exclusion criteria were as follows: (I) patients diagnosed with tumors before the onset of AP, (II) patients with AP due to an alternative etiology (including gallstone, alcohol, hyperlipidemia, etc.), (III) patients with chronic pancreatitis, and (IV) patients who had missing data as outlined in the Variables section.

The included patients were followed up by various methods (including hospital notes, telephone, WeChat and/or e-mail) from date of tumor diagnosis until death, or 1 December 2019, depending on which occurred first. AP without tumor (controls) were selected from the AP database, which had been described elsewhere (11,12), using stratified random sampling. Controls were matched to each study subject by gender and length of stay at a 1:4 ratio. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Institutional Committee of Ethics of Peking Union Medical College Hospital (S-K900), and individual consent for this retrospective analysis was waived.

Measures and outcomes

Demographic variables, including age, gender, medical history, alcohol, and tobacco consumption were abstracted. Clinical data included mortality, severity of AP, length of hospital stay, intensive care unit (ICU) admission, local complications, systematic complications, and laboratory data on admission. Acute Physiologic Assessment and Chronic Health Evaluation (APACHEII) was calculated 48h after presentation. Haemoglobin (HGB) below 110 g/L for female or 120 g/L for male was defined as anemia (13). Main pancreatic duct (MPD) dilatation on CT was defined by an MPD with a maximal diameter greater than 3 mm (14). Vascular invasion on CT was defined as the fat disappeared between the mass and adjacent vessels, the mass wrapped around more than 180° of the circumference of the adjacent vessels, and blood vessels were observed with stenosis (15). The database was set up and independently checked by two authors (Y Xiong and Y Zhao).

Procedures

The ICD code was adopted to retrieve patients diagnosed with AP [ICD 10 code (K85)] and tumor [ICD 10 code (C00)-(D48)] at Peking Union Medical College Hospital from 1 January 2000 to 1 December 2018. Eligible patients were selected based on the inclusion criteria and exclusion

Table 1 General characteristics of patients with tumors (n=103) presenting acute pancreatitis

Characteristics	Outcome
Age (years)*	57 [13–81]
Sex (male)	65 (63.1%)
HCT (%)†	36.9 (37.9)
Cr (umol/L)†	74.8 (68.0)
BUN (mmol/L)†	4.9 (4.4)
Severity (RAC)	
MAP	92 (89.3%)
MSAP	7 (6.8%)
SAP	4 (3.9%)
Local complications	
Acute peripancreatic fluid collection	11 (10.7%)
Acute necrotic collection	6 (5.8%)
Walled-off necrosis	0
Infected necrosis	0
Pancreatic pseudocysts	6 (5.8%)
Organ failure	
Multiple organ failure	1 (0.9%)
Respiratory failure	2 (1.9%)
Renal failure	3 (2.9%)
Shock	0
APACHE II (48 h)†	4.8 (3.7)
Ranson†	0.9 (0.8)
SIRS	5 (4.9)
ICU admission	4 (3.9)
Length of stay (days)*	18 [2–60]
Mortality due to AP	0
Mortality due to tumor	47 (45.6%)

Values in parentheses are percentages unless indicated otherwise; *values are median [range] and †values in mean (s.d.). RAC, Revised Atlanta Classification; MAP, mild AP; MSAP; moderately severe AP; SAP, severe AP; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; SIRS, systematic inflammatory response syndrome; ICU, intensive care unit.

criteria. We extracted clinical data from the hospital's electronic medical records and followed up the prognosis of tumor by hospital notes, telephone, WeChat and/or e-mail. Two persons established the database independently, and the inconsistencies were submitted to senior physicians for review and decision. The control group who were without tumor, was matched with contemporaneous patients with AP by 1:4 ratio who were randomly selected from the AP database which had been described elsewhere.

Statistical analysis

We performed analyses to describe and summarize the distributions of variables. We use the Student's t test, Wilcoxon rank-sum test or Kruskal-Wallis test to compare continuous variables, and the Chi-square test or Fisher's exact test to compare categorical variables. Univariable and multivariable logistic regression analysis was then applied to identify clinical features for tumors. All statistical analysis was performed using SPSS® version 22 (IBM, Armonk, New York, USA). P values of <0.05 were considered to be statistically significant.

Results

Out of 1792 AP patients, we identified 103 with tumors who presented with AP as the admission diagnosis. All the tumors were diagnosed after admission with AP. The median age of the cohort was 57 (range, 13–81) years with 65 males. The main clinical characteristics of these patients were summarized in *Table 1*. Abdominal pain occurred in all 103 patients. Median weight loss was 6.5 (range, 2–30) kilograms in 82 patients and obstructive jaundice in 29. The severity grade of AP was mild in 92 patients, moderately severe in 7 and severe in 4. Smoking history was present in 21 patients and drinking history in 17.

Tumor types

Of these 103 patients, the most common tumor is pancreatic cancer (PC) (40/103), followed by periampullary carcinoma (PAC) (25/103), neoplastic pancreatic cysts (NPC) (22/103), non-Hodgkin's lymphoma (5/103), metastatic lung cancer (4/103), parathyroidoma (3/103), pancreatic neuroendocrine tumor (pNET) (2/103), multiple myeloma (2/103).

Histopathologically, adenocarcinoma (38 cases) accounted for the majority of pancreatic cancer, the other one was carcinoma, and one was cystadenocarcinoma. As for periampullary carcinoma, 10 cases were vater ampulla carcinoma, 8 cases were cholangiocarcinoma, and 7 cases were duodenal adenocarcinoma. Neoplastic pancreatic cysts included 17 cases intraductal papillary mucinous neoplasms

Table 2 Clinical characteristics of patients with different tumors

	Pancreatic Cancer (n=40)	Periampullary carcinoma (n=25)	Neoplastic pancreatic cysts (n=22)	Non- Hodgkin's lymphoma (n=5)	Metastatic lung cancer (n=4)	P
Demographic data						
Age (years)*	56 [29–81]	57 [33–80]	62 [13–79]	41 [25–66]	61 [57–66]	0.236
Sex (male)	24 (60.0%)	13 (52.0%)	19 (86.4%)	3 (60.0%)	4 (100.0%)	0.060
Presenting symptoms						
Abdominal pain	40 (100.0%)	23 (92.0%)	22 (100.0%)	4 (80.0%)	4 (100.0%)	0.094
Radiation pain	15 (37.5%)	6 (24.0%)	2 (9.1%)	1 (20.0%)	2 (50.0%)	0.095
Vomiting	10 (25.0%)	12 (48.0%)	9 (40.9%)	2 (40.0%)	1 (25.0%)	0.377
Jaundice	12 (30.0%)	14 (56.0%)	1 (4.5%)	1 (20.0%)	1 (25.0%)	0.003
Fever	1 (2.5%)	10 (40.0%)	2 (9.1%)	2 (40.0%)	4 (100.0%)	<0.001
Weight loss	33 (82.5%)	22 (88.0%)	15 (68.2%)	5 (100.0%)	3 (75.0%)	0.339
Morphological features						
Dilation of MPD	30 (75.0%)	14 (56.0%)	17 (77.3%)	2 (40.0%)	1 (25.0%)	0.035
Dilation of BD	19 (47.5%)	17 (68.0%)	1 (4.5%)	1 (20.0%)	1 (25.0%)	<0.001
Vascular invasion	20 (50.0%)	4 (16.0%)	3 (13.6%)	1 (20.0%)	0	0.004
Enlarged lymph glands	4 (10.0%)	0	0	2 (40.0%)	1 (25.0%)	0.008
Pancreatic mass on US	12 (30.0%)	1 (4.0%)	8 (36.4%)	1 (20.0%)	0	0.046
Pancreatic mass on CT	34 (85.0%)	3 (12.0%)	16 (72.7%)	1 (20.0%)	4 (100.0%)	<0.001
Admission bloods						
HGB (g/L)†	128.9 (15.6)	123.6 (16.9)	133.0 (13.1)	99.3 (15.0)	100.8 (21.7)	0.002
HCT (%)†	38.3 (4.4)	37.1 (4.8)	38.5 (3.8)	29.6 (5.3)	29.5 (7.3)	0.001
DBIL (µmol/L)†	41.1 (77.6)	64.5 (65.8)	11.0 (28.9)	57.6 (48.1)	6.4 (3.6)	0.003
Cr (µmol/L)†	70.5 (17.8)	68.4 (22.8)	65.4 (15.4)	65.0 (15.6)	53.7 (31.4)	0.186
BUN (mmol/L)†	4.4 (1.7)	5.1 (1.9)	5.0 (2.1)	4.7 (2.5)	5.2 (3.2)	0.330
Tumor markers						
CEA (ng/mL)†	3.9 (6.5)	5.9 (7.2)	2.5 (1.2)	NA	3.8 (1.7)	0.491
CA 19-9 (u/mL)†	1,047.6 (3,096.7)	1,110.2 (2,565.1)	20.4 (33.5)	NA	38.3 (22.0)	<0.001

Values in parentheses are percentages unless indicated otherwise; *values are median [range] and †values in mean (s.d.). MPD, main pancreatic duct; BD: bile duct; US, ultrasonography; CT, computed tomography; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; NA, not available.

(8 cases of invasive), 3 cases serous cystadenomas, and 2 cases solid-pseudopapillary neoplasms. Among the 5 cases of non-Hodgkin's lymphoma, 4 cases were diffuse large B lymphoma, 1 case was T-cell lymphoma. As for metastatic lung cancer, 4 cases were all small cell lung cancer.

Clinical characteristics of patients with different tumors

The clinical characteristics of AP patients with different tumors were summarized in *Table 2*. Besides, there were 18 patients with a dilated MPD and/or vascular invasion but

Table 3 Clinical outcomes of patients with different tumors

	Pancreatic Cancer (n=40)	Periampullary carcinoma (n=25)	Neoplastic pancreatic cysts (n=22)	Non- Hodgkin's lymphoma (n=5)	Metastatic lung cancer (n=4)	P
Days from AP onset to diagnosis of tumor*	93 [11–489]	41 [4–946]	426 [8–3,324]	29 [2–57]	106 [99–112]	<0.001
AJCC stages						<0.001
Stage I	18 (45.0%)	7 (28.0%)	8 (36.4%)	0	0	
Stage II	1 (2.5%)	9 (36.0%)	0	1 (20.0%)	0	
Stage III	11 (27.5%)	5 (20.0%)	0	1 (20.0%)	0	
Stage IV	10 (25.0%)	4 (16.0%)	0	3 (60.0%)	4 (100.0%)	
Surgery due to tumor	27 (67.5%)	22 (88.0%)	18 (81.8%)	1 (20.0%)	1 (25.0%)	0.003
Chemotherapy	15 (37.5%)	2 (8.0%)	1 (4.5%)	5 (100.0%)	4 (100.0%)	<0.001
Mortality due to AP	0	0	0	0	0	–
Mortality due to tumor	25 (62.5%)	11 (44.0%)	1 (4.5%)	4 (80.0%)	3 (75.0%)	<0.001
Survival (months)‡	10.0 (7.0–23.5)	21.0 (5.0–37.0)	35.0 (30.0–96.0)	8.5 (2.0–36.0)	8.5 (5.3–15.5)	<0.001

Values in parentheses are percentages unless indicated otherwise; *values are median [range] and ‡values in median (IQR). AP, acute pancreatitis; AJCC, American Joint Committee on Cancer.

without a mass reported by computed tomography (CT). As for pancreatic cancer, the detection rates of mass by CT were 17.6%, 29.4%, 38.2%, 55.9% and 70.6% at the 1st week, 2nd week, 4th week, 8th week, and 12th week from the onset of AP, respectively.

In addition, three patients were diagnosed with functional parathyroid adenoma (PTH 193–629 pmol/L) and two with multiple myeloma. AP was caused by hypercalcemia (2.72–4.89 mmol/L) in all the five patients, including two cases of severe acute pancreatitis. There were two cases of pNET, of which the symptoms were not specific, mainly presented as abdominal pain, vomiting and pancreatic mass on CT.

Clinical outcome of patients with different tumors

The clinical outcome of patients with tumor-associated acute pancreatitis were summarized in *Table 3*. The median survival time of AP patients with PC was 10.0 (7.0–23.5) months. All patients with parathyroidoma recovered after surgical resection of the adenoma. These patients were followed up for up to 3 years or more, and no AP recurred. Patients with multiple myeloma received chemotherapy, and both of them died (survival time was 1 month and

13 months, respectively). Of these two pNET patients, one improved after surgery, while the other died in 27 months due to disease progression.

Diagnostic clues for patients with different tumors presenting acute pancreatitis

Due to the heterogeneity among tumors, we took the primary abdominal tumors (pancreatic cancer PC, periampullary carcinoma PAC, and neoplastic pancreatic cysts NPC) as a tumor group, which accounted for the largest proportion (87, 84.5%), to compare with the control group that patients having AP without tumor (*Table 4*).

The incidence of MSAP, SAP, organ failure, ICU admission, and APACHE II score were lower in the tumor group ($P<0.05$). The per cent of age above 50, weight loss, anemia, dilation of main pancreatic duct (MPD), and vascular invasion in the tumor group were higher than in the control group ($P<0.05$).

Multivariable logistic regression analysis revealed that patients with dilation of MPD (OR 417.83, 95% CI: 80.40–2,171.42, $P<0.001$), vascular invasion (OR 82.04, 95% CI: 6.05–1,113.14, $P=0.001$), mild AP (OR 8.29, 95% CI: 1.98–

Table 4 Comparison of clinical characteristics between AP patients with and without tumors (matched by 1:4 ratio)

	AP with tumor (n=87)	AP without tumor (n=348)	P
Age (years)			<0.001
≤50	18 (20.7)	168 (48.3)	
>50	69 (79.3)	180 (51.7)	
Sex (male)	56 (64.4%)	221 (63.5%)	0.881
Jaundice	27 (31.0%)	126 (36.2%)	0.366
Fever	13 (14.9%)	53 (15.2%)	0.947
Weight loss	70 (80.5%)	13 (3.7%)	<0.001
Anemia	20 (23.0%)	29 (8.3%)	<0.001
Cr (μmol/L)[†]	68.7 (18.5)	106.8 (87.8)	<0.001
BUN (mmol/L)[†]	4.8 (1.9)	6.0 (4.0)	0.008
Dilation of MPD	61 (70.9%)	2 (0.6%)	<0.001
Vascular invasion	27 (31.0%)	1 (0.3%)	<0.001
Severity(RAC)			<0.001
MAP	80 (92.0%)	206 (59.2%)	
MSAP	6 (6.9%)	73 (21.0%)	
SAP	1 (1.1%)	69 (19.8%)	
Local complications	19 (21.8%)	70 (20.1%)	0.721
Organ failure	1 (1.1%)	74 (21.3%)	<0.001
APACHE II (48h)[†]	4.2 (2.3)	5.7 (5.3)	0.010
Length of stay (days)*	19 [2–60]	18 [1–134]	0.386
ICU admission	1 (1.1%)	49 (14.1%)	0.001
Mortality due to pancreatitis	0	10 (2.9%)	0.195

Values in parentheses are percentages unless indicated otherwise; *values are median [range] and [†]values in mean (s.d.). Abbreviations: MPD, main pancreatic duct; RAC, Revised Atlanta Classification; MAP, mild AP; MSAP; moderately severe AP; SAP, severe AP; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ICU, intensive care unit.

34.73, P=0.004), and anemia (OR 5.73, 95% CI: 2.02–16.26, P=0.001) were independently associated with the presence of a tumor (*Table 5*).

Discussion

This study had identified four variables in patients presenting with AP that were independently associated with

Table 5 Factors independently associated with tumor pre-existing acute pancreatitis: Multivariable logistic regression analysis

Variable	Wald	OR	95% CI	P
Dilation of MPD	51.32	417.83	80.40-2,171.42	<0.001
vascular invasion	10.97	82.04	6.05–1,113.14	0.001
Mild AP	8.38	8.29	1.98–34.73	0.004
Anemia	10.75	5.73	2.02–16.26	0.001

MPD, main pancreatic duct; CI, confidence interval; OR, odds ratio.

a tumorous etiology: dilatation of the main pancreatic duct, vascular invasion, mild AP, and anemia. These variables represent clues for the diagnosis of tumor-associated AP. Moreover, it showed that AP can be an early presenting sign of a series of tumors even before the tumor itself is diagnosed, and if AP had been appropriately investigated, it might result in an earlier diagnosis of tumor. When compared to patients with AP but without tumor, we found that the severity of AP in the tumor group was more likely to be mild, which was similar to the study by Yohei Minato and Terumi Kamisawa (16).

The factors that should alert the clinician to suspect underlying tumors in patients who present with AP was largely unknown. In a previous study by Mujica and Barkin, patients with PC who presented with AP were generally older than 50 years of age and 89% was mild AP (17). Tanasijtchouk *et al.* (18) suggested that recurrent pancreatitis without identifiable cause, particularly in elderly patients accompanied by elevated bilirubin, should raise the suspicion of periampullary tumors. Jang *et al.* (5) reported that AP caused by IPMN was more likely to be mild. Several other authors had described acute pancreatitis as a reporting sign of pancreatic neuroendocrine tumor (pNET), non-Hodgkin's lymphoma (NHL), lung cancer, parathyroidoma, and multiple myeloma in case reports (4,7,8,19,20). But these studies did not include patients with a whole range of neoplastic causes and did not compare AP patients with and without the presence of a tumor. In the present study, we found that pancreatic cancer (PC), periampullary carcinoma (PAC), neoplastic pancreatic cysts (NPC) were the most common causes for tumor-associated AP, which accounted for more than 80% in this cohort, followed by non-Hodgkin's lymphoma (NHL), lung cancer, parathyroidoma, pancreatic neuroendocrine tumor (pNET), and multiple myeloma.

It was worth noting that diagnostic delay was common in

our cohort, taking an average of 93 days from the onset of AP to detect pancreatic cancer. There are Several reasons could account for the delay. First of all, it was well known that abdominal ultrasonography was suboptimal as the initial radiologic assessment for pancreatic tumors, for it was less sensitive and highly operator-dependent. Another possible explanation was that physicians tended to accept a common etiology (premature closure), such as gallstones or alcohol, rather than to search for a preexisting tumor, due to the lack of specific characteristics in the early stage of these tumors (2,10). Finally, the use of CT, especially contrast-enhanced CT, was not a routine diagnostic workup for AP patients, particularly in mild cases. Even if applied, diffuse pancreatic inflammation can mask a localized mass in the acute setting (21,22). Cho et al. argued that AP patients who had no clear etiology should routinely receive CT within three months after discharge in order to reveal underlying tumor (23). In our study, the overall sensitivity of CT in detecting pancreatic tumor was 85%, which was significantly higher than that of ultrasonography (30%). The detection rates by CT were 17.6%, 29.4%, 38.2%, 55.9% and 70.6% at week 1, 2, 4, 8, and 12 from the onset of AP, respectively. Our data supported conclusions by other authors that those idiopathic AP patients should be closely followed after discharge to avoid missed diagnosis of pancreatic tumors. If possible, such investigations should be performed after an interval of 3 to 4 weeks or scheduled follow-up at least within three months after discharge to allow for resolution of inflammatory changes secondary to the pancreatitis episode (23). Furthermore, we noted that in the present study, about one third of patients with PC remained undetectable in three months after discharge. Our finding justified a longer period of follow-up (six months to one year) particularly for those high-risk patients presented with older age, dilated pancreatic duct, anemia, and vascular abnormalities.

Acute pancreatitis had been previously reported as a favorable prognostic indicator in patients with tumors (24,25). A plausible explanation was that without AP these patients would have been easily overlooked due to no specific symptoms. And if AP had been appropriately investigated, it might result in an earlier diagnosis and, as a consequence, a better outcome (9). In a large national retrospective cohort study, Kirkegard et al. (25) investigated 12,522 patients with PC in Denmark and 37,522 patients in the United States (US) over a 13-year period. These patients were divided into two groups, cases with AP before PC and those without AP (179 vs. 12,343 cases in Denmark,

2,207 vs. 35,345 cases in the US). In the Danish cohort, the proportion of low-grade PC was higher (24.6% vs. 14.7%) in the AP group than the control group, surgical resection rate was also higher (20.1% vs. 12.1%), and the survival period longer (6.9 vs. 3.9 months). In the US cohort, the proportion of low-grade PC was higher (38.9% vs. 28.8%) in the AP group than the control group, but the ratio of surgical resection (16.1% vs. 11.3%) and the survival period (3.9 vs. 3.8 months) were comparable between the two groups. In our study, the median survival of PC patients was 10.0 months, which was significantly higher than PC patients without AP in the Danish and US cohort [10.0 (7.0–23.5) vs. 3.9 (1.3–10.8) months, P<0.001, 10.0 (7.0–23.5) vs. 3.8 (1.3–9.8) months, P<0.001, respectively], and was even higher than PC patients with AP in the two cohorts [10.0 (7.0–23.5) vs. 6.9 (2.0–15.3) months, P<0.001, 10.0 (7.0–23.5) vs. 3.9 (1.3–11.0) months, P<0.001, respectively] (25). It may be attributed to a high proportion of low-grade PC and a high surgical resection rate in our patients.

The underlying mechanisms of tumor-associated AP were unclear. There were several pathogenetic hypotheses: (I) mechanical obstruction of the pancreatic duct due to the mass, lymphadenopathy or poor pancreatic juice drainage, (II) pancreatic ischemia caused by vascular compromise secondary to tumor invasion, (III) secondary to hypercalcemia caused by tumor (4,5,19). In a series of 66 patients, 75.8% had pancreatic neoplasms and almost 40% of these patients had obstruction of the MPD (26). In our study, more than two thirds of patients had dilated pancreatic duct, approximately a quarter of patients had vascular infiltration, and less than one tenth had peripancreatic lymphadenopathy or hypercalcemia, which was consistent with previous reports. We postulated that as tumor-associated AP was mainly the consequence of mass effect, which usually developed over months or even years, it was not surprising that most AP episodes in these patients were mild and self-limited. But when AP was caused by hypercalcemia, it could be severe as seen in one patient with parathyroidoma and the other with multiple myeloma in our cohort.

The major strengths of our study included a reasonable sample size comprising different types of tumors, and we used a matched control group to identify the reporting signs and diagnostic clues for pre-existing tumors. Limitations of the study must be noted. First, it was a single-center retrospective study so we expected that our findings could be validated in other studies. Second, different tumors had variable clinical manifestations and pathogenesis, making it

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difficult to elaborate and compare the characteristics among all types of tumors. Last but not least, the retrospective nature of this study made a certain survival bias inevitable. Needless to say that future multi-center prospective studies were eagerly awaited to address these limitations.

In summary, our study highlighted the need of improved diagnostic workup and regular follow-up in high-risk patients, such as age above 50, without identifiable causes, with mild AP, anemia, dilation of MPD, and vascular invasion, in whom timely surveillance was crucial to reveal the underlying tumor.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-7196

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Ethicsal Statement: The authors were accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Institutional Committee of Ethics of Peking Union Medical College Hospital (S-K900), and individual consent for this retrospective analysis was waived.

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